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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,918	03/13/2001	Jean-Michel Dayer	UGEN:009US	8922

32425 7590 04/06/2007

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/803,918	DAYER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-62,66,70 and 74-77* is/are pending in the application.

4a) Of the above claim(s) *1-8,11-14,18-35,44,45 and 50-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-10, 15-16, 36-43, 46-49, 62, 66, 70 and 74-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

Notice to Comply	Application No. 09/803,918	Applicant(s) Jean-Michel Dayer	
	Examiner Phoung Huynh	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e). The correct SEQ ID NO:2 is present in the paper copy of the of the sequence listing only. Therefore a search of the correct sequence is not possible.

☒ 7. Other: SEQ. ID NO is required for sequences disclosed at page 65 lines 2 and 6 of the specification.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/22/07 has been entered.

2. Claims 1-16, 18-62, 66, 70 and 74-77 are pending.

3. Claims 1-8, 11-14, 18-35, 44-45, and 50-61 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 9-10, 15-16, 36-43, 46-49, 62, 66, 70 and 74-77, drawn to an isolated T-cell activation inhibitor polypeptide fragment of apo-A-I, a composition comprising said apo-A-I fragment, a fusion protein comprising said apo-A-I fragment and a process of making said apo-AI fragment are being acted upon in this Office Action.

5. In view of the amendment filed 1/22/07, all rejections from the previous Office Action mailed 10/23/06 are hereby withdrawn.

6. The following are new grounds of objection and rejections.

7. This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Amino Acid Sequence Disclosures. This application fails to comply with the sequence rules because SEQ ID NO is required for sequences "YGRKKRRQRRR" and GGGGYGRKKRRQRRR" disclosed at page 65, lines 2 and 6 of the specification, respectively.

8. Claim 15 is objected to because of the "polypeptide" in claim 15 at line 11 is inconsistent with the "polypeptide fragment" in claim 15 at line 1. This objection could be obviated by inserting the word "fragment" after "polypeptide" in claim 15, at line 11.

9. Claims 36, 40 and 46 are objected to because the limitation "polypeptide" should have been "polypeptide fragment" since the base claim 15, line 1 recites "polypeptide fragment". This objection could be obviated by inserting the word "fragment" after "polypeptide" in claims 36, 40, and 46 at line 1.

10. Claims 37, 42, and 48 are objected to because the limitation "polypeptide" should have been "polypeptide fragment" since the base claim 16, line 1 recites "polypeptide fragment". This objection could be obviated by inserting the word "fragment" after "polypeptide" in claims 37, 42 and 48 at line 1.

11. Claim 41 is objected to because the limitation "polypeptide" should have been "polypeptide fragment" since the base claims 40 and 15, line 1 recites "polypeptide fragment". This objection could be obviated by inserting the word "fragment" after "polypeptide" in claim 41 at line 1.

12. Claim 43 is objected to because the limitation "polypeptide" should have been "polypeptide fragment" since the base claims 42 and 16, line 1 recites "polypeptide fragment". This objection could be obviated by inserting the word "fragment" after "polypeptide" in claim 43 at line 1.

13. Claim 75 is objected to because the "polypeptide" in claim 75 part (a) through (e) is inconsistent with the "polypeptide fragment" in claim 75, line 1. This objection could be obviated by inserting the word "fragment" after "polypeptide" in claim 75 part (a) through (e).

14. Claim 77 is objected to because the "polypeptide" in claim 77 part (1) through (5) is inconsistent with the "polypeptide fragment" in claim 77, line 1. This objection could be obviated by inserting the word "fragment" after "polypeptide" in claim 77 part (1) through (5).

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 46-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated polypeptide fragment of apo-A-I *consisting of the amino acid sequence* selected from the group consisting of: (a) the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) the amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) the amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) the amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO: 2 and (e) the amino acid sequence as set forth in residues 73 to 113 of SEQ IDNO: 2, wherein the polypeptide fragment inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes that were stimulated through contact with the membrane of T lymphocytes, (2) a composition comprising the isolated polypeptide fragment mentioned above and a pharmaceutically acceptable formulation agent comprises at least one of a carrier, adjuvant, solubilizer, stabilizer, or anti-oxidant, (3) the polypeptide fragment mentioned above, which is covalently modified with a water-soluble polymer such as the ones recited in claims 40-41, (4) A fusion polypeptide comprising the polypeptide fragment mentioned above and a heterologous amino acid sequence, **does not** reasonably provide enablement for (1) any and all IgG constant domain fragment thereof, and (2) any and all alkaline phosphatase fragment thereof fused to any apo-A-I polypeptide fragment for the claimed fusion protein as set forth in claims 46-49. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 46 and 48 encompass any and all *alkaline phosphatase fragment* fused to an isolated T-cell activation inhibitor polypeptide fragment of apo-A-I for the claimed fusion protein.

Enablement is not commensurate in scope with claims as how to make and use any alkaline phosphatase fragment in the claimed fusion protein.

The specification discloses only polypeptide fragment of human apolipoprotein A-I (apo-A-I) selected from the group consisting of the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2 (FIG. 1B); the amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2 (FIG. 1C); the amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2 (FIG. 1D); the amino acid sequence as set forth in residues 73 to 113 wherein the polypeptide fragment inhibits tumor necrosis factor (TNF) or interleukin 1 (IL-1) production by monocytes that were stimulated through contact with T lymphocytes, specification at pages 4-5 and 91-98. The inhibitory activity of Apo-I fragment was mainly directed to the activating factors expressed at the surface of stimulated T cells, see page 99-100. The specification discloses fusion protein comprising the T-cell activation inhibitor polypeptide fragment mentioned above fused to a heterologous amino acid sequence such as epitope tag, an IgG constant domain, an alkaline phosphates, a tat protein or a FLAG epitope, see specification at paragraphs [0477], [0267] and [0259].

The specification does not teach how to make and use any and all fragment of any enzyme alkaline phosphatase without the structure of the alkaline phosphatase fragment for the claimed fusion protein. There is not a single fragment from the smallest to the largest fragment shows any enzyme activity. There is a lack of working example showing that any undisclosed alkaline phosphatase fragment fused to any polypeptide fragment of apo-A-I retains its enzyme activity, in turn, useful for detection assays. The actual biological activity of the enzyme fragment in the fusion protein remains to be demonstrated.

While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants useful as alkaline phosphatase requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of deletion variants maintains structure and enzyme activity. However, the problem of predicting functional aspects of the product from mere sequence data and what changes can be tolerated is complex and well outside the realm of routine experimentation. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that

the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

The state of the art as exemplified by the teachings of Ngo *et al* is such that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Michigami et al (Eur J Pediatr 164: 277-282, 2005; PTO 892) teach that a deletion in the gene encoding alkaline phosphatase such as F310del mutation led to an almost complete loss of enzymatic activity while a substitution from F at position 310 to L (F310L) retains around 70% of enzymatic activity compared with normal wild-type protein (see page 7280, col. 2, Fig. 2, in particular). Without such guidance, the fragments of alkaline phosphatase which can be made and retain enzymatic activity for the claimed fusion protein is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Claims 46-49 encompass any and all *IgG constant domain fragment* fused to an isolated T-cell activation inhibitor polypeptide fragment of apo-A-I as set forth in claims 15 and 16 for the claimed fusion protein.

Enablement is not commensurate in scope with claims as how to make and use any IgG constant domain fragment in the claimed fusion protein.

The specification does not teach how to make and use any and all fragment of IgG constant domain without the structure of the IgG constant domain fragment for the claimed fusion protein. There is not a single fragment from the smallest to the largest fragment of IgG constant fusion protein show increasing *in vivo* half-life. There is a lack of working example showing that any undisclosed IgG fragment fused to any polypeptide of apo-A-I mentioned above maintains its structure and retaining or extending the *in vivo* half-life of the fusion protein.

Zuckier et al (Cancer Research 58: 3905-3908, 1998; PTO 892) teach knowledge of structural features that control half-life is invaluable in designing immunological molecules. Despite this importance, mechanisms and structures that regulate immunoglobulin half-life have only recently begun. Zuckier et al teach multiple constant regions of IgG1 are involved in the regulation of immunoglobulin half-life, either exerting their effects by conformational changes on

the CH2 and CH3 domains, altered susceptibility on all three regions hinge CH2-CH3 domain of the IgG contributed to the overall rate of catabolism. Zuckier et al further teach deletion of any of the constant domain of IgG2b results in the shortening rather than increasing the intravascular half-life either directly or by inducing conformational changes elsewhere in the molecule (see page 3907, col. 2, last paragraph, in particular). Without such guidance, the fragments of IgG constant domain fragment which can be made and retain which function for the claimed fusion protein is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

17. Claims 46-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any and all IgG constant domain fragment, and (2) any and all alkaline phosphatase fragment fused to the apo-A-I polypeptide fragment for the claimed fusion protein as set forth in claims 46-49.

The specification discloses only polypeptide fragment of human apolipoprotein A-I (apo-A-I) selected from the group consisting of the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2 (FIG. 1B); the amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2 (FIG. 1C); the amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2 (FIG. 1D); the amino acid sequence as set forth in residues 73 to 113 wherein the

polypeptide fragment inhibits tumor necrosis factor (TNF) or interleukin 1 (IL-1) production by monocytes that were stimulated through contact with T lymphocytes, specification at pages 4-5 and 91-98. The inhibitory activity of Apo-I fragment was mainly directed to the activating factors expressed at the surface of stimulated T cells, see page 99-100. The specification discloses fusion protein comprising the T-cell activation inhibitor polypeptide fragment mentioned above fused to a heterologous amino acid sequence such as epitope tag, an IgG constant domain, an alkaline phosphates, a tat protein or a FLAG epitope, see specification at paragraphs [0477], [0267] and [0259].

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed fragment of IgG Fc domain and fragment of any alkaline phosphatase in the claimed fusion protein and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The amino acid sequence of the region of the IgG Fc domain or the amino acid sequence of the enzyme fragment having the specific activity is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

With the exception of the specific full length IgG constant domain and alkaline phosphatase fused to the specific fragment of apolipoprotein A-I (apo-A-I) having the specific inhibitory activity mentioned above, there is insufficient written description about the structure associated with function of any and all IgG constant domain *fragment*, and any and all enzyme alkaline phosphatase *fragment* for the claimed fusion protein. There is not a single fragment of any IgG constant domain other than the Fc fragment in the specification as filed.

Zuckier et al (Cancer Research 58: 3905-3908, 1998; PTO 892) teach deletion of any of the constant domain of IgG2b results in the shortening rather than increasing the intravascular

half-life; this shorting intravascular half-life is either directly or by inducing conformational changes elsewhere in the molecule (see page 3907, col. 2, last paragraph, in particular).

Likewise, there is not a single fragment from the smallest to the largest fragment of alkaline phosphatase shows any enzyme activity in the specification as filed.

Michigami et al (Eur J Pediatr 164: 277-282, 2005; PTO 892) teach that a deletion in the gene encoding alkaline phosphatase such as F310del mutation led to an almost complete loss of enzymatic activity while a substitution from F at position 310 to L (F310L) retains around 70% of enzymatic activity compared with normal wild-type protein (see page 7280, col. 2, Fig. 2, in particular). As such, the structure of any fragment of any IgG constant domain and the structure of any fragment of any alkaline phosphatase in the claimed fusion protein are not adequately described.

The specification discloses only the full-length IgG constant domain Fc fragment and the enzyme alkaline phosphatase, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of fragment of IgG constant domain and fragments of any enzyme alkaline phosphates to describe the genus for the claimed fusion protein. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 9-10, 15-16, 36-39 and 75-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmidt et al (J Biol Chem 270(10): 5469-5475, 1995; PTO 892).

Schmidt et al teach a fragment of the mature secreted human apo-A-I such as apoA-I^{201} wherein the reference fragment has a truncation of 66 amino acids, which is at least 50 amino acids shorter relative to the claimed human apo-A-I fragment of SEQ ID NO: 2 (see Figure 2, page 5470, col. 2, Results, in particular). The reference apoA-I^{201} fragment corresponds to the

claimed (residues 25 to 225 of SEQ ID NO: 2) lacking a prepropeptide at the amino terminus which corresponds to the first 24 amino acids of the claimed SEQ ID NO: 2 and a truncation of 42 amino acids from the carboxy terminus which corresponds to (residues 226 to 267 of claimed SEQ ID NO: 2), see Figure 2 truncation indicated by arrow 201, page 5469, col. 2, first full paragraph, in particular).

The terms "comprising" and "fragment being encoded by a vector comprising a nucleic acid molecule consisting of a nucleotide" are open-ended. It expands the polypeptide fragment of amino acid residues 25 to 194, or 25 to 144, or 25 to 113, or 73 to 113 of SEQ ID NO: 2 to include additional amino acids at either or both ends as long as the fragment is at least 50 amino acids shorter and contained the specified portions of SEQ ID NO: 2 to include the reference fragment. Further, when the transitional phrase "consisting of" appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded in the claim as a whole. The transition language "comprising" allowed the claims to cover the entire sequence plus other portions of the plasmid, as long as the nucleotide sequence contained the specific portion of SEQ ID NO: 2 recited by the claims. *Mannesmann Demag Corp. v. Engineered Metal Products Co.,* 793 F.2d 1279, 230 USPQ 45 (Fed. Cir. 1986). >See also *In re Crish*, 393 F.3d 1253, 73 USPQ2d 1364 (Fed. Cir. 2004), *Id.*, 73 USPQ2d at 1365. In determining the scope of applicant's claims directed to "a purified oligonucleotide comprising at least a portion of the nucleotide sequence of SEQ ID NO:1 wherein said portion consists of the nucleotide sequence from … to 2473 of SEQ ID NO:1, and wherein said portion of the nucleotide sequence of SEQ ID NO:1 has promoter activity," the court stated that the use of "consists" in the body of the claims did not limit the open-ended "comprising" language in the claims (emphases added). *Id.* at 1257, 73 USPQ2d at 1367, see MPEP 2111.03.

Because the reference truncated apoA-I^{201} fragment corresponding to the claimed (residues 25 to 225 of SEQ ID NO: 2) has a truncation of at least 66 amino acids and retains the specific claimed amino acid residues 25 to 194, or 25 to 144, or 25 to 113, or 73 to 113 of SEQ ID NO: 2, the reference truncated apoA-I^{201} fragment inherently has the same inhibitory activity such as inhibiting T cell activation or inhibiting tumor necrosis factor (TNF) or interleukin-1 produced by monocytes. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims

are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Schmidt et al also teach the a process of making the reference truncated apoA-I^{201} fragment by providing a prokaryotic cell such as *E coli* comprising a vector such as pMal-c/AI comprising the cDNA encoding the reference truncated mutant and a DNA encoding the maltose binding protein for ease of purification, culturing the host cell and isolating the reference truncated apoA-I^{201} fragment by column chromatograph, and cleaving off the maltose binding protein to obtain the purified apo-A-I (see page 5470, col. 1, Expression and purification of Recombinant ApoA-I, in particular). The reference apo-A-1 is encoded by the reference vector pMal-c/AI. Schmidt et al further teach a composition comprising the reference purified apoA-I^{201} fragment without the maltose binding protein and a pharmaceutically acceptable agent or carrier such as distilled water H_2O (see page 5470, col. 1, last paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

20. Claims 9-10, 15-16, 36-39 and 75-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Borhani et al (Proc Nat Acad Sci USA 94: 12291-12296, November 1997; PTO 892).

Borhani et al teach a fragment of the mature secreted human apo-A-I such as apo Δ (1-43) that has a truncation of 67 amino acid acids from the N terminus relative to the claimed SEQ ID NO: 2 (see FIG. 3, apo Δ (1-43) which contains residues 44-243 of the claimed SEQ ID NO: 2, page 12291, col. 2, abbreviations, in particular). The reference secreted mature apo-A-I is 243 amino acids in length lacking the prepro peptide which is the first 24 amino acids of the claimed SEQ ID NO: 2 plus the deletion of 1-43 which corresponds to residues 25-51 of claimed SEQ ID NO: 2. The reference apo Δ (1-43) fragment corresponds to residues 68-267 of claimed SEQ ID NO: 2 (see sequence in FIG. 3, in particular).

The terms "comprising", "fragment being encoded by a vector comprising a nucleic acid molecule consisting of a nucleotide", and "encoding" are open-ended. It expands the claimed amino acid residues 73 to 113 or 156 to 267 of SEQ ID NO: 2 to include additional amino acids at either or both ends to include additional amino acids at either or both ends as long as the fragment has a truncation of at least 50 amino acids from either the N or C terminus and contained the specified portions of SEQ ID NO: 2 to include the reference fragment. Further, when the transitional phrase "consisting of" appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other

elements are not excluded in the claim as a whole. The transition language "comprising" allowed the claims to cover the entire sequence plus other portions of the plasmid, as long as the nucleotide sequence contained the specific portion of SEQ ID NO: 2 recited by the claims. *Mannesmann Demag Corp. v. Engineered Metal Products Co.*, 793 F.2d 1279, 230 USPQ 45 (Fed. Cir. 1986). >See also *In re Crish*, 393 F.3d 1253, 73 USPQ2d 1364 (Fed. Cir. 2004), *Id.*, 73 USPQ2d at 1365. In determining the scope of applicant's claims directed to "a purified oligonucleotide comprising at least a portion of the nucleotide sequence of SEQ ID NO:1 wherein said portion consists of the nucleotide sequence from … to 2473 of SEQ ID NO:1, and wherein said portion of the nucleotide sequence of SEQ ID NO:1 has promoter activity," the court stated that the use of "consists" in the body of the claims did not limit the open-ended "comprising" language in the claims (emphases added). *Id.* at 1257, 73 USPQ2d at 1367, MPEP 2111.03.

Because the reference amino terminus truncated apo Δ (1-43) fragment has a truncation of at least 67 amino acids at the amino terminus and retains the claimed amino acid residues 73 to 113 or 156 to 267 of SEQ ID NO: 2 (see FIG 3, in particular), the reference truncated apo Δ (1-43) fragment inherently has the same inhibitory activity such as inhibiting T cell activation or inhibiting tumor necrosis factor (TNF) or interleukin-1 produced by monocytes. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fec. Cir. 1990). See MPEP 2112.01.

Borhani et al also teach a process of making the reference truncated apo Δ (1-43) fragment by providing a prokaryotic cell such as *E coli*, culturing the host cell to produce the reference truncated apo Δ (1-43) fragment and purifying truncated apo Δ (1-43) fragment by reverse-phase HPLC (see page 12291, Methods, in particular). The reference host cell *E coli* necessarily contains a plasmid comprising a cDNA that encodes the reference truncated apo Δ (1-43) fragment since *E coli* bacteria does not produce human truncated apo Δ (1-43) on its own. Borhani et al further teach a composition comprising the reference purified apo Δ (1-43) and a pharmaceutically acceptable formulation agent or carrier such as 1.2 M sodium citrate (see page 12292, col. 1, first paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

21. Claims 9-10, 15-16, 36-39, 62, 66, 70, and 74-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Pyle et al (Biochemistry 35, 12046-12052, 1996; PTO 892).

Pyle et al teach various truncated human proapolipoprotein AI such as proapoAI-6-135 that has 107 amino acids truncated from the carboxy terminus which corresponds to residues 19-160 of claimed SEQ ID NO: 2 (see page 12048, col. 2, last paragraph, in particular) or proapoAI-6-150 that has 92 amino acids truncated from the carboxy terminus which corresponds to residues 19-175 of claimed SEQ ID NO: 2 (see page 12049, col. 1, in particular). Pyle et al teach ApoAI is initially synthesized as a preproapolipoprotein. The first 18 amino acid prepeptide is cleaved as the apoAI is translocated across the membrane of the endoplasmic reticulum and the 6 residue propeptide is subsequently removed in the plasma to form the mature apo-A-I is 243 amino acids in length (see page 12046, col. 2, in particular). The reference truncated proapoAI-6-135 (corresponding to 19-160 of claimed SEQ ID NO: 2) has the first 18 amino acids at the amino terminus removed and 107 amino acids truncated from the carboxy terminus. The reference proapoAI-6-150 (corresponding to 19-175 of claimed SEQ ID NO: 2) fragment has first 18 amino acids at the N terminus removed and 92 amino acids truncated from the carboxy terminus.

The terms "comprising", "fragment being encoded by a vector comprising a nucleic acid molecule consisting of a nucleotide", and "encoding" are open-ended. It expands the claimed amino acid residues 25 to 113, or 73 to 113 or 25 to 144 of SEQ ID NO: 2 to include additional amino acids at either or both ends to include the reference proapoAI-6-150 fragment. Likewise, the term "comprising" expands the claimed residues 25 to 113, or 73 to 113 of SEQ ID NO: 2 to include to include additional amino acids at either or both ends to include the reference proapoAI-6-135 fragment. Further, when the transitional phrase "consisting of" appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded in the claim as a whole. The transition language "comprising" allowed the claims to cover the entire sequence plus other portions of the plasmid, as long as the nucleotide sequence contained the specific portion of SEQ ID NO: 2 recited by the claims. *Mannesmann Demag Corp. v. Engineered Metal Products Co.,* 793 F.2d 1279, 230 USPQ 45 (Fed. Cir. 1986). >See also *In re Crish*, 393 F.3d 1253, 73 USPQ2d 1364 (Fed. Cir. 2004), *Id.*, 73 USPQ2d at 1365. In determining the scope of applicant's claims directed to "a purified oligonucleotide comprising at least a portion of the nucleotide sequence of SEQ ID NO:1 wherein said portion consists of the nucleotide sequence from … to 2473 of SEQ ID NO:1, and wherein said portion of the nucleotide sequence of SEQ ID NO:1 has promoter activity," the

court stated that the use of "consists" in the body of the claims did not limit the open-ended "comprising" language in the claims (emphases added). *Id.* at 1257, 73 USPQ2d at 1367, MPEP 2111.03.

Because the reference apo A-I fragments have a truncation of at least 50 or at least 75 amino acids at the carboxy terminus and contain the specific claimed amino acid residues 25 to 113, or 73 to 113 or 25 to 144 of SEQ ID NO: 2, the reference truncated proapoAI-6-150 fragment and proapoAI-6-135 fragment inherently have the same inhibitory activity such as inhibits tumor necrosis factor (TNF) or interleukin-1 produced by monocytes. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fec. Cir. 1990). See MPEP 2112.01.

Pyle et al also teach a process of making the reference truncated proapoAI-6-135 fragment and proapoAI-6-150; each is produced by obtaining prokaryotic host cell such as *E coli* comprising a vector such as pGEX-KN vector comprising the cDNA encoding the reference truncated mutant and GST; culturing the host cell under conditions suitable to express the encoded polypeptide and isolating the proapoAI-6-135 fragment and proapoAI-6-150 by cleaving off the GST with thrombin (see page 12047, Materials and Methods, Construction of Recombinant plasmids, col. 1, Expression or Recombinant apoAI, col. 2, in particular). Pyle et al further teach the truncated proapoAI-6-135 fragment and proapoAI-6-150 fragment each can be produced in eukaryotic cell such as insect cell/baculovirus expression system (see page 12046, col. 2, last paragraph, in particular). Pyle et al teach a composition comprising the reference purified truncated proapoAI-6-135 or proapoAI-6-150 and a pharmaceutically acceptable carrier such as PBS (see page 12047, col. 2, last paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

24. Claims 15-16 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (J Biol Chem 270(10): 5469-5475, 1995; PTO 892) or Borhani et al (Proc Natt Acad Sci USA 94: 12291-12296, November 1997; PTO 892) or Pyle et al (Biochemistry 35, 12046-12052, 1996; PTO 892) each in view of US Pat No. 5,824,784 (of record, Oct 1998; PTO 892).

The teachings of Schmidt et al, Borhani et al and Pyle et al have been discussed supra.

The claimed invention as recited in claims 40 and 42 differs from the teachings of the references only in that polypeptide is covalently modified with a water-soluble polymer.

The claimed invention as recited in claims 41 and 43 differs from the teachings of the references only in that polypeptide is covalently modified with a water soluble polymer wherein the water soluble polymer is selected from polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

The '784 patent teaches method and composition for covalently modified any polypeptide of interest such as G-CSF or INF with a water-soluble polymer such as polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol (See abstract, column 6, lines 32-67 bridging column 7, lines 1-5, column 9, lines 64-66, in particular). The '784 patent further teaches various pharmaceutically acceptable formulation agent or carrier such as phosphate buffer, adjuvant, solubilizer such as Tween 80, anti-oxidants such as ascorbic acid, and sodium metafisulfate (See column 11, lines 11-32, in particular). The '784 patent teaches the advantages of N-terminally pegsylated protein are that it provides a homogeneous preparation to ease in clinical application, with predictability of lot to lot pharmacokinetics for desired dosage,

increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modify the apo-A-I polypeptide fragment apoA-I^{201} as taught by Schmidt et al or the apo Δ (1-43) as taught by Borhani et al or the proapoAI-6-150 and proapoAI-6-135 fragments as taught by Pyle et al with any one of the water soluble polymer as taught by the '784 patent and then formulates the composition in pharmaceutically acceptable carrier such as phosphate buffer, solubilizer such as Tween 80 or stabilizer or antioxidant as taught by the '784 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the advantages of N-terminally pegsylated protein are that it provides a homogeneous preparation to ease in clinical application, with predictability of lot to lot pharmacokinetics for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity as taught by the '784 patent (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

25. Claims 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (J Biol Chem 270(10): 5469-5475, 1995; PTO 892) in view of US 5,420,247 (May 30, 1995; PTO 892) or US Pat No 5,565,335 (Oct 1996; PTO 892).

The teachings of Schmidt et al have been discussed supra. Schmidt et al further teach a fusion polypeptide comprising a fragment of the mature apo-A-I such as apoA-I^{201} fused to a maltose binding protein for ease of purification (see page 5470, col. 1, Expression and Purification of Recombinant ApoA-I, Caption in FIG 1, in particular). Schmidt et al further teach the reference truncated apoA-1 had a remarkably increased rate of catabolism, when compared with the normal apoA-I and altered its plasma clearance (see page 5471, col. 2, first paragraph, in particular).

The invention differs from the teachings of the reference only in that a fusion polypeptide comprising the polypeptide fragment as set forth in claims 15 or 16 and fused to a heterologus amino acid sequence from an IgG constant domain.

The '247 patent teaches an isolated fusion molecule comprising a human IgG Fc constant region fused to an autoantigen polypeptide sequence such as human LIFR (See Figure 3, col. 12, line 36, col. 14, lines 43-52, col. 13, line 55-63, claim 4 of '247 patent, in particular). The '247 patent teaches that IgG Fc fusion molecule can easily be purified using protein A or protein G affinity chromatography (See col. 33, lines 35-47, in particular).

The '335 patent teach fusion molecule comprising a Ig constant domain such as human IgG1 Fc fused to CD4 or myelin associated glycoprotein (See col. 4, Detailed description, lines 18-31, in particular). The reference Fc fusion molecule enhances the plasma half-life of the fusion molecule and is useful for (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to fuse apoA-I^{201} as taught by Schmidt et al to the IgG constant domain as taught by the '247 patent or the '335 patent to form a fusion polypeptide comprising the apoA-I^{201} and IgG Fc by substituting the human LIFR in the Fc fusion protein as taught by the '247 patent for the apoA-I^{201} as taught by Schmidt et al or by substituting the CD4 or myelin associated glycoprotein in the IgG1 Fc fusion protein as taught by the '335 patent for the apoA-I^{201} as taught by Schmidt et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '247 patent teaches that IgG Fc fusion molecule can easily be purified using protein A or protein G affinity chromatography (See col. 33, lines 35-47, in particular). Schmidt et al teach the truncated apoA-1 had a remarkably increased rate of catabolism (short half-life) when compared with the normal apoA-I and altered its plasma clearance (see page 5471, col. 2, first paragraph, in particular). The '335 patent teach Fc fusion molecule enhances the plasma half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

26. Claims 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pyle et al (Biochemistry 35, 12046-12052, 1996; PTO 892) in view of US 5,420,247 (May 30, 1995; PTO 892) or US Pat No 5,565,335 (Oct 1996; PTO 892).

The teachings of Pyle et al have been discussed supra. Pyle et al further teach due to the influence of apoAI on the development of atherosclerosis, the focus of attention is to identify the

important structural and functional elements within the apoAI protein sequence (see page 12046, col. 1 and 2, in particular). Pyle et al further teach the carboxy-terminal portion of the apoAI emerged as an important contributor to the secondary structure of this protein such as formation of trimer and dimer (see page 12051, col. 1, 3rd full paragraph, page 12051, col. 2, first paragraph, in particular).

The invention differs from the teachings of the reference only in that a fusion polypeptide comprising the polypeptide fragment as set forth in claims 15 or 16 and fused to a heterologus amino acid sequence from an IgG constant domain.

The '247 patent teaches an isolated fusion molecule comprising a human IgG Fc constant region fused to an autoantigen polypeptide sequence such as human LIFR (See Figure 3, col. 12, line 36, col. 14, lines 43-52, col. 13, line 55-63, claim 4 of '247 patent, in particular). The '247 patent teaches that IgG Fc fusion molecule can easily be purified using protein A or protein G affinity chromatography (See col. 33, lines 35-47, in particular).

The '335 patent teach fusion molecule comprising a Ig constant domain such as human IgG1 Fc fused to CD4 or myelin associated glycoprotein (See col. 4, Detailed description, lines 18-31, in particular). The reference Fc fusion molecule enhances the plasma half-life of the fusion molecule and is useful for (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to fuse the truncated proapoAI-6-135 or proapoAI-6-150 fragment as taught by Pyle et al to the IgG constant domain as taught by the '247 patent or the '335 patent to form a fusion polypeptide comprising either proapoAI-6-135 or proapoAI-6-150 and IgG Fc by substituting the human LIFR in the Fc fusion protein as taught by the '247 patent for the proapoAI-6-135 or proapoAI-6-150 as taught by Pyle et al or by substituting the CD4 or myelin associated glycoprotein in the IgG1 Fc fusion protein as taught by the '335 patent for the proapoAI-6-135 or proapoAI-6-150 as taught by Pyle et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '247 patent teaches that IgG Fc fusion molecule can easily be purified using protein A or protein G affinity chromatography (See col. 33, lines 35-47, in particular). Pyle et al teach the carboxy-terminal portion of the apoAI emerged as an important contributor to the secondary structure such

as formation of trimer and dimer of this protein (see page 12051, col. 1, 3rd full paragraph, page 12051, col. 2, first paragraph, in particular). The '335 patent teach Fc fusion molecule enhances the plasma half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

27. No claim is allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

29. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
March 30, 2007